Autologous bone marrow cells for avascular necrosis femoral head

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Abstract

Avascular necrosis (AVN) of the femoral head can be a devastating progressive disease most commonly affecting patients younger than 40 years of age. Although the exact pathophysiology of AVN has yet to be elucidated, the disease is characterized by a vascular insult to the blood supply of the femoral head, which can lead to collapse of the femoral head and subsequent degenerative changes. If AVN is diagnosed in the early stages of the disease, it may be possible to attempt surgical procedures which preserve the hip joint, including decompression of the femoral head augmented with concentrated bone marrow. The use of autologous stem cells has shown promise in halting the progression of AVN of the femoral head, and subsequently preventing young patients from undergoing total hip arthroplasty. We studied five patients of stage 2 osteonecrosis of femoral head with core decompression and insertion of autologous mononuclear cells with aseptic precautions. There was significant reduction in pain and joint symptoms with no further radiological progression in 12 months of follow up.

Keywords: Avascular necrosis, Concentrated bone marrow, Femoral head, Osteonecrosis, Stem cells.

Introduction

Avascular necrosis (AVN, also known as osteonecrosis) of the femoral head occurs when the cells of the trabecular bone spontaneously die, leading to fracture[(1)]. Depending on the amount of femoral head involved, collapse of the articular surface will occur[(1,2)]. Once collapse of the femoral head occurs in these patients, severe pain ensues, and the disease course rarely regresses. Although the pathogenic process is poorly understood, osteonecrosis is the final common pathway of traumatic and non-traumatic insults and compromises the already precarious circulation of the femoral head. Magnetic resonance imaging is important in the diagnosis of hip osteonecrosis as well as in predicting the outcome. The primary therapeutic strategy by which these patients experience pain relief is total hip arthroplasty (THA), but at a younger age than in patients undergoing THA for degenerative arthritis. The replicative capacities of osteoblastic cells obtained from the intertrochanteric area of the femur are reduced in patients with osteonecrosis[(6)]. The number and the activity of fibroblast colony-forming units, reflecting the number of mesenchymal stem cells that could potentially give rise to mature osteoblasts have been shown to be decreased in osteonecrosis [(7,8)].

Pathophysiology of AVN The pathophysiology of AVN remains unclear despite many attempts to provide a theoretical model[(9,10)]. However, there are several recognized conditions and environmental insults that can predispose patients to AVN (Table 1). Although these factors may increase a patient's risk for developing AVN, others propose that the disease results from a clotting disorder or genetic abnormality that leads to vascular compromise[(11)]. Another working hypothesis asserts that the cell death is due to increased intramedullary pressure in the femoral head, leading to decreased blood flow and cell death via a mechanism similar to compartment syndrome following a traumatic injury[(12)]. Often an underlying cause cannot be determined. However, these idiopathic cases may actually be attributable to clotting abnormalities or collagen mutations[(11,13)].

Jones et al found that approximately 82% of patients in their study had at least one coagulation factor abnormality[(11)]. Similarly, Liu et al noted that a COL2A1 gene mutation in certain families predisposed to development of AVN[(13)].

Table 1: Risk factors for avascular necrosis of the femoral head

Traumatic/Direct Injury	Non-traumatic
Femoral neck/head fracture	Corticosteroid use
Hip dislocation	Alcohol abuse
Slipped capital femoral epiphysis	Idiopathic
	Sickle cell disease
	Caisson disease
	Cushing's disease
	Non-Traumatic
	Systemic lupus erythematosus
	Organ transplantation
	Prior radiation therapy
	Smoking
	Pregnancy
	Chronic pancreatitis
	Coagulopathy
	Chronic renal failure
	Lipid disorders

Autologous Bone marrow concentrate: Spontaneous regression of AVN is rare, with the vast majority of untreated patients progressing to THA. It is thought that, in patients with AVN, there is an insufficient supply of progenitor cells located in the femoral head and proximal femur to remodel the area of necrosis[14]. Although options to halt the progression of AVN are available (core decompression, osteotomy, medical treatments), the results have been disappointing, with up to 40% of patients progressing to THA[15]. Since progenitor cells may be lacking in the lesioned area, newer treatment modalities have been developed to introduce stem cells to the areas of necrosis in an attempt to prevent fracture and collapse by restoring the architecture of the femoral head.

Core decompression is still the most widespread procedure to treat early stages of osteonecrosis of the femoral head. Notwithstanding the fact that this procedure has been used for more than four decades, its efficacy remains controversial. Indeed, in randomized controlled trials, the efficacy of core decompression measured in terms of decreased proportion of patients having additional surgeries or showing delayed radiological progression to collapse could not be demonstrated. Therefore, there have been attempts to treat osteonecrosis by implantation of stem cells into the necrotic lesion or by utilizing growth factors[16]. The rationale for this approach is based on our present patho-physiological understanding of the sequence of events in osteonecrosis.

Autologous bone-marrow transplantation was reported for the first time in a patient suffering from osteonecrosis of the humeral head due to sickle cell anemia with improvement of pain and range of motion and reconstruction of the humeral epiphysis[17]. Thereafter, Hernigou et al. and Gangji et al. studied the efficacy of bone marrow implantation into the necrotic lesion of osteonecrosis of the femoral head[13]. Gangji et al. studied 13 patients (eighteen hips) with stage-I or II (without subchondral fracture) osteonecrosis of the femoral head according to the Association Research Circulation Osseous classification in a controlled double blind trial with 24 months of follow-up[18].

The hips were allocated to a program of core decompression only (control group) or core decompression and implantation of bone marrow mononuclear cells (bone marrow graft group). After 24 month follow up, there was a significant reduction in pain and joint symptoms within the bone marrow graft group (p=0.021). At 24 months, 5 of the 8 hips in the control group had deteriorated to stage-III (stage of the subchondral fracture), whereas only one of the 10 hips in the bone marrow graft group had progressed to this stage (p=0.016). Survival analysis showed a significant difference in the time to collapse between the two groups. Moreover, in the bone marrow graft group, the volume of the necrotic lesion decreased by 35% after 24 months. Similarly, Hernigou and Beaujean reported the results of a prospective study of 189 hips in 116 patients treated with core decompression and bone marrow grafting[17].

Material and Methods

Five patients of stage 2 AVN head of femur were recruited into study according to FICAT staging. They were followed up for a period of 12 months. The average age at surgery was 33 (22-44) and there were 4 male patient and one female patient. There were 3 cases from steroid and 2 cases from idiopathic origin. The duration of pre-operative symptoms was 11 to 18 (14.5 months) months.

Around 120 ml bone marrow was harvested from Posterior superior iliac spine in lateral position of patient (Fig. 2) after proper aseptic precautions taken in OT. Heparin treated 20 ml syringes is used to collect the sample. Bone marrow then placed in sterile blood bag of 150 ml. using the cold centrifuge machine, the mononuclear cells were separated in operation theatre.

After changing the patient position into supination the fracture table is attached and part preparation for core decompression is being done. Decompression by drilling into necrotic site of femoral head done (Fig. 3), the finally separated mononuclear cell cocktail is pushed in the decompression site after tilting the other hip down. Opening on bone sealed with bone wax. For six weeks patient was instructed to walk with walker (no weight bearing on affected sire).

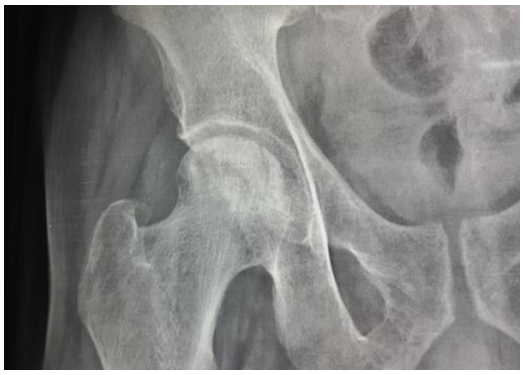

Fig. 1: Pre-Operative x-ray Rt Hip

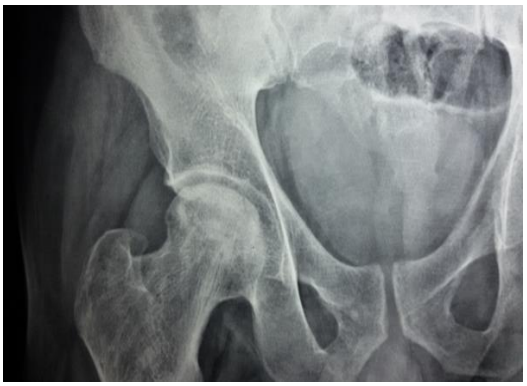

Fig. 2: X-ray right hip after 12 months post operatively

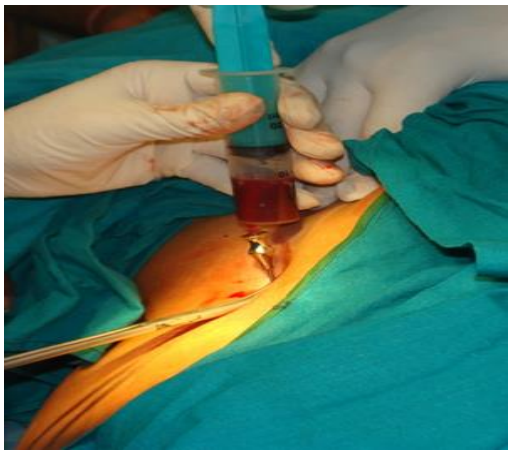

Fig. 3

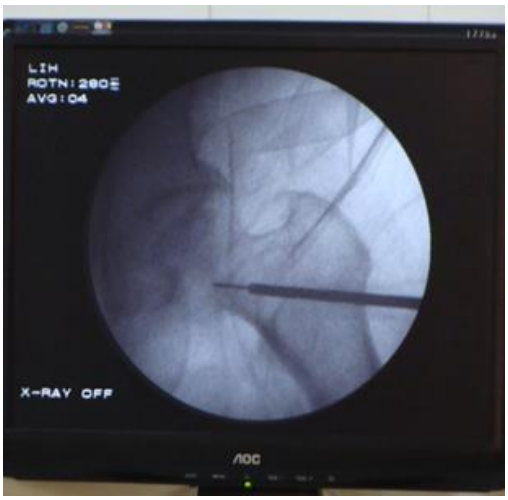

Fig. 4

Results

Over all significant decrease in the pain level was detected with no further radiographic deterioration in next 12 months postoperatively. (Pre op x-ray 1 and Post op x-ray 2) Post operatively patients were given antibiotics for 2 weeks and no clinical evidence of infection developed. Overall there was decrease in hip joint pain and there was significant increase in Joint movement .Further long term follow up is desirable.

Discussion

Core decompression is the gold standard technique for the treatment of early-stage AVN of the femoral head and in stage 2 onwards it might decrease the fast progression of disease if with core decompression the mononulealar cells are injected. There are a number of patient specific factors that might be considered when determining the outcome of the disease and the treatment such as stage of disease, various risk factors, lesion size, age, life expectancy health comorbidities and activity level. However, new insights into the pathophysiology of osteonecrosis as a concurrent bone and vascular disease and treatment modifications based on this understanding show promise in the arrest of complications from early osteonecrosis. Nevertheless, there remain some controversy about the ability of core decompression to influence the outcome of osteonecrosis. Recent advances suggest that a decrees in mesenchymal stem cell pool of the proximal aspect of femur might not provide enough osteoblasts to meet the needs of bone remodelling in early stage of disease[19]. An insufficiency of osteogenic cells could explain the inadequate repair mechanism that, it is postulated, leads to femoral head collapse. The effectiveness of bone marrow mononuclear cells may be related to availability of stem cells endowed with osteogenic properties, arising from an increase in supply of such cells to the femoral head through bone marrow mononuclear cell cocktail implantation. Indeed, in the very early stages of osteonecrosis providing sufficient repair capacity through the implantation of osteogenic cells could make lesion reversible[20,21]. Another possible explanation for the therapeutic effect of implantation is that injected marrow stromal cells secrete antigenic cytokines resulting in increased angiogenesis and subsequent improvement in osteogenesis.one study has suggested that the efficacy of such implantation was due to a supply of endothelial progenitor cells included in CD34 fractious well as to multiple antigenic factors released from CD34 fractions[22].

Although the findings of this study are promising, their interpretation is limited by the constraints imposed by the relatively small number of patients and the short duration of follow up. The bone marrow mononuclear cells were injected in decompression site and some of noble mononuclear cells might have leaked out through hole on bone. Larger trials and other techniques are needed to confirm and fully understand our results.

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